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Pharmacokinetics of Nicotine, Cotinine, and 3′-Hydroxycotinine in Cigarette Smokers

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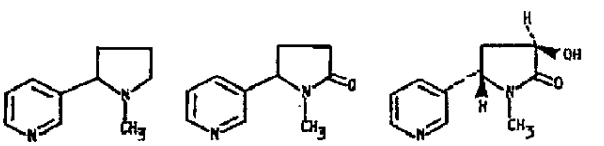
Summary. The trans-isomer of 3′-hydroxycotinine has recently been identified as a major metabolite of nicotine in urine of cigarette smokers. We, therefore, investigated the pharmacokinetics of 3′-hydroxycotinine in six male smokers after intravenous infusion of nicotine, cotinine, and 3′-hydroxycotinine. Serum concentrations of 3′-hydroxycotinine were lower than those of cotinine throughout the observation period of 60 h after infusion of nicotine or cotinine, whereas the amounts excreted in the urine were similar or higher than those of cotinine. The following means and ranges for the pharmacokinetic parameters were derived from the 3′-hydroxycotinine infusion experiment: half-life ($t_{1/2\,\beta}$) = 5.9 (4.2–9.5) h; apparent volume of distribution (V_d) = 0.87 (0.51–1.14) l/kg; total clearance (Cl_{total}) = 1.79 (1.08–2.59) ml/min/kg; renal clearance (Cl_r) = 1.31 (0.85–1.78) ml/min/kg; percentage of renal clearance (Cl_r/Cl_{total}) = 75.4 ± 12.8 (60.3–98.2). The high percentage of renal clearance suggests that further metabolization of this compound is limited. No evidence for a mutagenic activity of 3′-hydroxycotinine or of urine extracts from subjects dosed with hydroxycotinine was found with the *S. typhimurium* (TA 98) microsome assay.

Key words: Nicotine – Cotinine – 3′-Hydroxycotinine – Pharmacokinetics – Intravenous infusion – Male smokers

Introduction

In the early 1960s McKennis et al. reported on the occurrence of hydroxycotinine in urine of smokers [17] and a nonsmoker to whom cotinine was orally administered [4]. Hydroxycotinine was also detected as a metabolite of nicotine and cotinine in other species [5, 15, 16, 25]. It was not before 1972 however that Dagne and Castagnoli [6] identified the stereochemical structure of metabolic hydroxycotinine as trans-1-methyl-3(R)-hydroxy-5(S)-3-pyridyl-2-pyrrolidinone (in the following referred to as 3′-hydroxycotinine). Recently,



Kyerematen et al. [13] reported that in rats 4.5% of the radiolabelled nicotine administered was recovered as 3′-hydroxycotinine in the urine. By measuring 13 metabolites, including nicotine, these authors were able to trace 70% of the dose applied. Nicotine, cotinine, nicotine-1′-N-oxide, cotinine-N-oxide, and nornicotine accounted for 11.3%, 7.2%, 11.6%, 9.3%, and 8,9%, respectively. Neurath et al. [19] quantified 3′-hydroxycotinine in urine of cigarette smokers. The relative amounts of six metabolites determined in the urine of nine smokers smoking medium nicotine cigarettes (0.9 mg/cigarette) were as follows: nicotine 21%, cotinine 17%, nicotine-1′-N-oxide 5%, nornicotine 2%, N-methylnicotinium ion 2%, and 3′-hydroxycotinine 53%. According to these results, 3′-hydroxycotinine has to be regarded as a principal metabolite of nicotine in smokers. Therefore, we investigated the pharmacokinetics of this compound after infusion of nicotine, cotinine, and 3′-

Abbreviations: A_e = amount of unchanged drug in the urine; AUC = area under curve; C = blood concentration at zero time; Cl_r = renal clearance; Cl_{total} = total clearance; S. = Salmonella; SD = standard deviation; S9-mix = supernatent after 9000 x *g* centrifugation of liver homogenate; $t_{1/2\,\alpha}$ = initial half-life; $t_{1/2\,\beta}$ = terminal half-life; V_d = apparent volume of distribution

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